



**UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/082,112 05/20/98 MENDOZA A MSU4.1-406

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HM12/0824

EXAMINER

TURNER, S

ART UNIT

PAPER NUMBER

1647

DATE MAILED:

08/24/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Advisory Action

Application No.
09/082,112

Applicant(s)

Mendoza

Examiner

Sharon L. Turner, Ph.D.

Group Art Unit

1647



THE PERIOD FOR RESPONSE: [check only a) or b)]

- a) ☐ expires _____ months from the mailing date of the final rejection.
- b) ☐ expires either three months from the mailing date of the final rejection, or on the mailing date of this Advisory Action, whichever is later. In no event, however, will the statutory period for the response expire later than six months from the date of the final rejection.

Any extension of time must be obtained by filing a petition under 37 CFR 1.136(a), the proposed response and the appropriate fee. The date on which the response, the petition, and the fee have been filed is the date of the response and also the date for the purposes of determining the period of extension and the corresponding amount of the fee. Any extension fee pursuant to 37 CFR 1.17 will be calculated from the date of the originally set shortened statutory period for response or as set forth in b) above.

- ☒ Appellant's Brief is due two months from the date of the Notice of Appeal filed on 5-3-00 (or within any period for response set forth above, whichever is later). See 37 CFR 1.191(d) and 37 CFR 1.192(a).

Applicant's response to the final rejection, filed on 08-14-00 and 4-18-00 has been considered with the following effect, but is NOT deemed to place the application in condition for allowance:

- ☒ The proposed amendment(s):

☐ will be entered upon filing of a Notice of Appeal and an Appeal Brief.

☒ will not be entered because:

- ☒ they raise new issues that would require further consideration and/or search. (See note below).
- ☐ they raise the issue of new matter. (See note below).
- ☒ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal.
- ☐ they present additional claims without cancelling a corresponding number of finally rejected claims.

NOTE: The proposed amendments to claim 18 raise new issues that would require further consideration.

- ☐ Applicant's response has overcome the following rejection(s):

- ☐ Newly proposed or amended claims _____ would be allowable if submitted in a separate, timely filed amendment cancelling the non-allowable claims.

- ☒ The affidavit, exhibit or request for reconsideration has been considered but does NOT place the application in condition for allowance because:

The proposed amendment has not been entered. All rejections are maintained for the reasons of record.

- ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

- ☒ For purposes of Appeal, the status of the claims is as follows (see attached written explanation, if any):

Claims allowed: None

Claims objected to: None

Claims rejected: 16-27

- ☐ The proposed drawing correction filed on _____ ☐ has ☐ has not been approved by the Examiner.

- ☐ Note the attached Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

- ☒ Other See attached Advisory Action

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Advisory Action

1. The Art Unit of U.S. Patent application SN 09/082,112 has changed. In order to expedite the correlation of papers with the application please direct all future correspondence to Examiner Turner, Technology Center 1600, Art Unit 1647.
2. The amendment, declaration and IDS filed 3-14-00 have been received. The declaration filed 4-18-00 has been received. The amendment has not been entered because the proposed amendments raises new 112 second paragraph issues with respect to duplicative reference to "removed proteins" in dependent claims 19, 24 and 25 as previously set forth in the Advisory Action of 2-17-00. This raises the issue of improper antecedent basis and is indefinite with respect to the "removed proteins."
3. The IDS filed after final rejection on 3-14-00 has not been considered because the IDS was not accompanied by the appropriate petition, certified statement and fee, see in particular 37 CFR 1.97(d).
4. The declaration filed 3-14-00 is not persuasive. The declaration states that extracellular antigens are by definition never attached to the outside of the cell and are in fact detached from the cell, p. 1, last 2 lines spanning p. 2. Webster's Dictionary defines extracellular as occurring or found outside a cell. Levy teaches that β -lactamases are secreted into the extracellular environment, see in particular Figure 15-4 which shows β -lactamase depicted as a moon shaped protein traversing the lipoprotein cell membrane from intracellular to the extracellular space. Ahearn teaches extracellular proteinases of yeast and yeast-like fungi, an extracellular protease

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produced intracellularly by an organism as indicated by cleavage of casein by organisms plated on agar coated with casein, the extracellular enzyme being proteolytically active against casein. Tortora teaches that extracellular enzymes are released by bacteria into the surrounding medium. The examiner finds no reference to "extracellular" in Denys. Singleton teaches that extracellular with respect to enzymes refers to substances which are external, but not contiguous to the cell(s) that produced them and also teach that some author use the term to refer to substances or structures which are external to the cell wall whether or not they are contiguous to it. The examiner notes that Singleton allows for a definition wherein extracellular is used to describe proteins which are external to the cell wall but may be contiguous to it as set forth by Singleton. Further the examiner reiterates that whether or not the protein is eventually excreted by the cell as an extracellular protein, that the protein is made within the cell and is exported, thus the extracellular protein may be distinguished by its presence in the intracellular environment, for evidence all of the above point to extracellular proteins as being made by and released from the cell as set forth above and depicted in Figure 15-4 by Levy. Thus, the examiner maintains that applicants invention can not be distinguished by the terms separated intracellular proteins and separated extracellular proteins because the specification does not teach the exclusion of extracellular proteins from the inside of the cell as contained in the prior art references as previously set forth. The extracellular proteins are made and are present inside the cell. Thus, for these reasons applicants declaration is not persuasive.

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5. The declaration filed 4-18-00 is not persuasive. The declaration is improper with respect to formal matters as it is not directed to instant application but to a related application.

Nevertheless the declaration describes *P. insidiosum* vaccination studies in equines and a Thai boy. The declaration does not specify the particular vaccine preparation with respect to instant claims or with respect to the preparation of the prior art. In no instance is the declaration found relevant to the ability of the instantly claimed invention to be distinguished from the invention of the prior art in particular as it relates to separated intracellular and extracellular proteins. Thus, for these reasons applicants declaration is not persuasive.

Rejections Maintained

6. Claims 16-22 and 24-27 stand rejected under 35 U.S.C. 102(b) as set forth in Paper No. 10, as being anticipated by Mendoza et al, Mycopath. 119:83-93, 1992.

Applicants argue that "the extracellular antigens are separated from the cell mass and expressed into the culture medium. The extracellular antigens are not part of the outside of the cells as seems to be implied by the Office Action. The intracellular antigens are all of the antigens of the cell including any surface antigens." Applicants arguments are not persuasive. It appears that applicants are using recognized terms in the art contrary to their accepted meaning. Extracellular antigens are those antigens contained outside the cell. Intracellular antigens are those contained inside the cell. Proteins may be referred to as being intracellular or extracellular with reference to their normal location in the cell, i.e. generally intracellular proteins are wholly contained within the cell however, extracellular proteins are generally on the surface of the cell

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and are usually anchored by either some mechanism (another protein) or a portion of that protein which traverses the membrane. Some proteins are made in the cell and are exported or secreted from the cell. These proteins are generally referred to as secretory or excretory proteins. The examiner further notes that regardless of a proteins destined location, all proteins are made intracellularly and thus can at times be considered to be intracellular. The pending claims are drawn to mixed extracellular and mixed intracellular proteins, not antigens. Thus, contrary to applicants assertion, it is still unclear how the intracellular and extracellular proteins are distinguished from each other and moreover how they are distinguished from the protein vaccines of the prior art reference. (Both the CMV and SCAV vaccines are disclosed in Mendoza). The prior art reference provides that the vaccine proteins are subjected to ultrafiltration through a PM-10 membrane (MW cutoff 10,000 MW). This membrane effectively removes proteins with molecular weights lower than 10,000 MW as does dialysis. Applicants further argue through process limitations, that the protein vaccines of the prior art reference differ from the protein vaccine of instant claims. These arguments are not persuasive. There are no process limitations in the claims. Further, in response to applicants arguments with respect to solubility, one of skill in the art readily recognizes the property of solubility is determined by factors such as amino acid sequence structure and salt concentration. There is no recognition in the art that the soluble proteins after disruption are the intracellular proteins as applicants arguments imply. Disruption of cells releases both soluble intracellular as well as soluble extracellular proteins to solution, and these proteins would be contained in the soluble fraction of

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a lysate, regardless of the mode by which the cells were lysed, i.e., homogenization vs. sonication, etc. Thus, contrary to applicants assertion there appears to be no difference between the protein vaccines of the prior art reference and instant claims.

7. Claims 16-22 and 24-27 stand rejected under 35 U.S.C. 102(b) as being anticipated by Mendoza et al, J. Mycol. Med, 6:151-164.

Applicants argue that while the Mendoza vaccine contains the 28K, 30K and 32K intracellular antigens added to the SCAV vaccine that Mendoza does not teach the many other soluble intracellular antigens which are included in the vaccine of instant claims. These arguments are not persuasive for the reasons of record and further as set forth above. Mendoza teaches the CMV vaccine, the SCAV vaccine and a third vaccine wherein the 28K, 30K and 32K intracellular antigens are added to the SCAV vaccine. Thus clearly these vaccines contain mixed intracellular and mixed intracellular antigens which have been removed of proteins less than 10,000 MW by ultrafiltration through a PM-10 membrane. Thus, the vaccines of Mendoza are no different from instant claims.

8. Claims 23 and 26-27 stand rejected under 35 U.S.C. 103(a) as set forth in Paper No. 10 as being unpatentable over Mendoza et al., Mycopathol., 1992(a) (IDS Ref: AI), or Mendoza et al, J. Mycol. Med, 1996, in view of Mendoza et al J Clin Microbiol., Nov 1992, and Panella et al, Cancer Res., 50(14):4429-25.

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Applicants argue that the claimed vaccine exhibits unexpected results and that the claimed vaccine as distinguished over the vaccines of the prior art are thus not obvious over the prior art references.

These arguments are not persuasive. The examiner maintains as set forth above and in Paper No. 10, that the vaccine of instant claims are not distinguished over the prior art references. Claims 13, which involve killing by thimerosal and claims 26-27 which involve a further dialysis step were rejected as being obvious over the prior art references. The prior art reference teaches killing with Merthiolate the trade name of thimerosal. Panella is used to establish that the killing (preservative) properties of the compound were known in the art. In reference to the dialysis step applicant is referred to the discussion in the 102 rejection which teaches that the prior art references achieved the removal of proteins less than 10,000 molecular weight by the alternative method of ultrafiltration through a PM-10 membrane (Amicon, MW cutoff 10,000). Thus, these steps were rendered obvious over the prior art references. Thus the vaccine is obvious over the prior art references as set forth in the 102 and 103 rejections of record.

Status of Claims

9. No claims are allowed.

Conclusion

10. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice

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published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (703) 308-0056. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached at (703) 308-4623.

Sharon L. Turner, Ph.D.
August 21, 2000

Patricia A. Duffy
PATRICIA A. DUFFY
PRIMARY EXAMINER